REMARKS

Applicants have received and reviewed the Office action dated February 19, 2010. By way of response, Applicants have amended claims 1 and 18. Claim 24 has been cancelled. No new matter has been added. Claims 1-4, 6-9, 14-19, 21-23, 25 and 27-31 are pending. Applicants submit that the amended claims are supported by the specification as filed.

Claim 1 has been amended to incorporate recitations of claim 24. It has also been amended to recite "monolithic matrix dosage form...." Support for this recitation can be found in paragraphs [0038], [0080], [0081] of the US Publication 2007/0196396 of the instant application. Moreover, example 5, example 7, example 8 and example 9 of the as filed patent application depict monolithic matrix dosage forms.

For the reasons presented below the Applicants respectfully submit that the amended claims are in condition for allowance, and notification to that effect is earnestly solicited.

Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected Claim 18 under 35 USC § 112, second paragraph.

The Office Action suggested that claim 18 should depend from claim 15. Applicants acknowledge and appreciate this suggestion. Claim 18 has therefore been amended to be dependent from claim 15, as suggested by the Examiner.

Accordingly, Applicants respectfully submit that the amended claims fully comply with § 112, second paragraph, and withdrawal of this rejection is earnestly solicited.

Rejection of Claims under 35 U.S.C. § 103

1. The Examiner rejected claims 1-4, 6-9, 14-19 and 21-25 under 35 USC 103(a) as being unpatentable over FALK (US 4,803,081) and SHELL (US 5,972,389) in the view of PATEL (US 2003/0180352). Applicants respectfully traverse this rejection.

The Falk et al. Reference

According to the office action the difference between the rejected claims and FALK is that FALK does not expressly teach a gastric retentive dosage form, the swelling agent poly(ethylene oxide) or the swelling enhancer cross-linked polyvinylpyrrolidone. This deficiency in the swelling agent poly(ethylene oxide), according to the Office Action, is cured by

the teaching of SHELL and the deficiency in the swelling enhancer cross-linked polyvinylpyrrolidone is cured by the teaching of PATEL.

Falk et al. discloses an extended release preparation of an active compound with very low solubility containing the active compound dissolved or dispersed in a semi-solid or liquid non-ionic solubilizer (abstract). The active compound in Falk et al. is preferably dissolved or dispersed in the solubilizer and the mixture of the drug and the solubilizer is incorporated into a pharmaceutical formulation, which gives prolonged release. According to Falk et al. the active compound mixed with the solubilizer is incorporated into different kinds of known controlled release systems, e.g. a hydrophilic gel system, preferably a hydrophilic swelling matrix.

Though Falk et al. mentions incorporation of active mixed with the solubilizer in hydrophilic swelling systems it does not enable, teach, suggest or motivate in any manner the design and preparation of controlled release gastroretentive system of the present invention. Development of a gastroretentive system requires enormous efforts towards selection of excipients that would aid retention of the dosage form in the upper gastrointestinal tract for prolonged time. Not only is the selection of appropriate viscosity grades of hydrophilic swelling agents a prerequisite to the designing of a gastroretentive dosage form, but also selection of type and amount of other excipients that may be used along with them determines the performance of such gastroretentive dosage forms.

The instant invention incorporates a swelling enhancer along with the swelling agent, wherein the swelling agent, in combination with swelling enhancer, swells in the presence of water in gastric fluid such that the size of the dosage form is sufficiently increased to provide retention of the dosage form in the stomach of a patient, and gradually erode within the gastrointestinal tract over a prolonged time period. According to the invention, it has been surprisingly found that addition of swelling enhancers to the gastro-retentive swelling system reduces the swelling time considerably which can further aid in improving bio-availability of drugs with narrow therapeutic absorption window (*See* Paragraph [0051] of the U.S. Publication 2007/0196396).

Swelling enhancers are members of a special category of excipients that swell rapidly to a large extent resulting in a dramatic increase in the size of the tablet. At lower concentrations, these excipients are used as superdisintegrants; however at concentration above 5% w/w these agents function as swelling enhancers and help increase the size of the dosage form. The amount

of swelling enhancer that may be incorporated in the compositions of the present invention is, for example, about 5 to about 90 weight percent (See Paragraph [0077] and [0078] of the U.S. Publication 2007/0196396). Thus the agents listed in the instant invention as swelling enhancers can in fact work so when they are used in an amount of above about 5 weight percent.

In view of this, example 5 of Falk et al. cited by the Examiner, containing 1.29% microcrystalline cellulose which is cited under the list of swelling enhancers of the present invention and lactose 12.02% which is **not** listed under the list of swelling enhancers of the present invention (See Paragraph [0077] of the U.S. Publication 2007/0196396), can in essence be considered to be devoid of swelling enhancers since microcrystalline cellulose in Example 5 of Falk et al. is also employed below the required percent limit of definition of swelling enhancers of at least 5 weight percent in the present invention.

The difference between the rejected claims and Falk et al. is therefore that Falk et al. does not expressly teach gastric retentive dosage form, swelling enhancer and the swelling agent poly (ethylene oxide). Therefore the Applicants respectfully submit that the Falk et al. reference neither teaches nor suggests the presently claimed invention, and the shortcomings of this reference are not remedied by the secondary references Shell et al. and Patel et al.

The Secondary References Do Not Remedy the Shortcomings of the Falk et al. Reference

According to the office action the deficiency in the swelling agent poly (ethylene oxide) is cured by the teachings of SHELL and the deficiency in swelling enhancer cross-linked polyvinylpyrrolidone is cured by the teachings of PATEL.

In view of this the Applicants respectfully reiterate as in the response to the previous office action that Shell et al. teaches controlled release dosage form that comprises a tablet or capsule containing a plurality of particles of a solid-state drug dispersed in a swellable/erodible polymer that (i) swells unrestrained dimensionally via imbibition of gastric fluid to increase the size of the particles to promote gastric retention within the stomach of a patient in which the fed mode has been induced, (ii) gradually erodes over a time period of hours, with the erosion commencing upon contact with the gastric fluid, and (iii) releases the drug to the stomach and duodenum at a rate dependent on the erosion rate, such as poly (ethylene oxide). Once ingested, the tablet or capsule of Shell et al. is said to disintegrate to disperse the particles within the stomach where they imbibe water to cause them to swell and promote retention in fed-mode-

induced patients. As the gastric-retained particles gradually erode, the drug is released in a controlled manner to the stomach for treatment of local disorders, and to the upper gastrointestinal tract where it becomes available for absorption in a controlled manner. Thus, the dosage form of Shell et al. is multiparticulate type of a gastroretentive system (*See* Column 13, last paragraph of SHELL).

In contrast to controlled-release dosage form of Shell et al. comprising a plurality of solid particles or pellets of a solid-state drug dispersed within a polymer which upon ingestion rapidly dissolve or disintegrate upon contact with the gastric fluid to permit the particles to disperse in the stomach; the compositions of the present invention are monolithic matrix systems as recited in amended claim 1, which upon ingestion cause swelling of the entire dosage form administered resulting in retention of the dosage form in the upper gastrointestinal tract. Gastroretentive systems as of Shell et al. comprising plurality of particles tend to undergo faster gastric emptying than the compositions of the present invention.

Thus though Shell et al. utilizes a polymer like poly(ethylene) oxide, it does not teach, suggest or motivate the design of monolithic matrix type gastroretentive systems using the same that are retained in the upper gastrointestinal tract for a prolonged time. Further a person skilled in the art would not draw any motivation from the teachings of Shell et al. to design matrix type of gastroretentive systems wherein the dosage form does not disperse into particles or pellets upon ingestion in the stomach and the entire administered dosage form swells to a size that does not pass through the pyrolus and the dosage form is retained in the upper gastrointestinal tract for a time period of up to about 12 hours.

Therefore Shell et al. when combined with Falk et al. does not in any manner teach, suggest, motivate or provide the compositions of the presently claimed invention that incorporates solubilized active agent in a gastroretentive matrix having one or more swelling agents and one or more swelling enhancers and wherein the entire monolithic matrix dosage form administered swells to a size that does not pass through the pyrolus leading to retention of the dosage form in the stomach of the patient.

Further that the deficiency in swelling enhancer cross-linked polyvinylpyrrolidone is stated in the office action to be cured by the teachings of PATEL, cannot be considered so, as Falk et al. cannot be considered to teach a swelling enhancer in the first place.

Patel et al. discloses solid pharmaceutical compositions for improved delivery of a wide variety of active ingredients contained therein or separately administered that include a solid carrier being formed of different combinations of active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides and solubilizers. As has already been emphasized in the previous response to office action, Patel et al. does not in any manner discuss any swelling or gastroretentive type of a dosage forms. Moreover, Patel et al. does not disclose in any manner the use of swelling enhancers nor does it disclose the amount and the purpose of using the same as has been mentioned in the instant invention. Further Patel et al. includes cross-linked polyvinylpyrrolidone in its laundry list of additives and does not in any manner suggest its use as a swelling enhancer. Such a listing of cross-linked polyvinylpyrrolidone has been linked without any specificity to its use in the compositions of the present invention. Patel et al. in fact does not in any manner teach, motivate or suggest design of gastroretentive systems or the use of swelling enhancers and further in combination with Falk et al. alone or with Falk et al. and Shell et al. does not even motivate the compositions of the instant invention.

Accordingly based on the foregoing differences, Applicants respectfully submit that the cited references, neither alone nor in combination, teach nor suggest the presently claimed compositions. Moreover, in view of the amended claim 1, withdrawal of this rejection is earnestly solicited.

2. The Examiner rejected claims 27-31 under 35 U.S.C. 103(a) as being unpatentable over FALK (US 4,803,061) in view of DOSHI (US 2003/0232081). Applicants respectfully traverse this rejection.

According to the Examiner, the difference between the rejected claims and Falk et al. is that FALK does not teach a multi-layered expanding gastric retentive dosage form or the swelling enhancer cross-linked polyvinylpyrrolidone. Further, the Examiner states that the deficiencies in a multi-layered expanding gastric retentive dosage form and the swelling enhancer cross-linked polyvinylpyrrolidone are cured by the teachings of DOSHI.

In view of this rejection the Applicants respectfully emphasize that though the Examiner on page 13 of the current Office action states that the feature upon which the Applicant relies i.e. "gastroretention by relying on a single mechanism" is not recited in the rejected claim; the Applicants in view of this respectfully submit that the amendment in Claim 27 that was

introduced in the previous response to state "swelling multi-layered system" intended to indicate that swelling was used as a mechanism to achieve gastroretention.

Additionally, the Applicants respectfully submit that Doshi et al. does not in any manner cure the deficiency of use of swelling enhancer of Falk et al. Doshi et al. does not suggest the use of any swelling enhancer nor does it suggest the use of cross-linked polyvinylpyrrolidone as a swelling enhancer.

Doshi et al. discloses a solid pharmaceutical composition for oral administration containing two or more layers comprising of a) at least one layer containing an active agent and disintegrating agent intended for immediate delivery, b) at least one second layer that includes an active agent for controlled drug delivery, gas generating component, a matrix forming gelling agent which is intended for controlled delivery of active agent to maintain therapeutic effective concentrations with once a day administration in a human body. The first layer intended for immediate delivery of an active agent comprises of a disintegrating agent which can be selected from group of starch, sodium starch glycolate, pregelatinised starch, crosslinked poly vinyl pyrrolidone, cross linked carboxy methyl cellulose, ion exchange resin, the most preferred being sodium starch glycolate which is said to be present in an amount ranging from about 0.25% to 2.5%, more preferably 0.5 to 2.0% and most preferably is about 1% by weight based on the total weight of the composition. Doshi et al. thus discusses the use of cross-linked polyvinyl pyrrolidone as a disintegrant in the first immediate release layer but does not in any manner disclose the use of cross-linked polyvinylpyrrolidone as a swelling enhancer in the second layer meant for sustained or controlled delivery of the active agent. In fact, Doshi et al. does not disclose, enable, teach, suggest or motivate the use of swelling enhancers in the instant compositions and especially in the second sustained release swelling layer of the multilayer compositions of the present invention. Moreover Doshi et al. does not disclose, enable, teach, suggest or motivate the use of swelling enhancers at more than 5 weight percent in the instant compositions.

Further though the Examiner states that Doshi further teaches the pharmaceutical compositions of their invention can also comprise well known ingredients such as disintegrants, povidone [cross-linked polyvinylpyrrolidone], microcrystalline cellulose, sodium starch glycolate and starch, among others; it does in any manner suggest the use of any of these excipients in the form of swelling enhancers, particularly in the second layer meant for sustained

delivery of the active. Swelling enhancers according to the instant invention are excipients that swell rapidly to a large extent resulting in a dramatic increase in the size of the tablet. At lower concentrations, these excipients are used as superdisintegrants; however at concentration above 5% w/w these agents function as swelling enhancers and help increase the size of the dosage form. The amount of swelling enhancer that may be incorporated in the compositions of the present invention is about 5 to about 90 weight percent (See Paragraph [0077] and [0078] of the U.S. Publication 2007/0196396). Doshi et al. does not in any manner disclose such a use of any of its listed excipients mentioned. Doshi et al. also does not disclose, teach, enable, suggest or motivate that addition of swelling enhancers to the gastro-retentive swelling system reduces the swelling time considerably.

Accordingly based on the foregoing differences, Applicants respectfully submit that the cited references neither alone nor in combination, teach nor suggest the presently claimed compositions and withdrawal of this rejection is earnestly solicited.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers or any future reply, if appropriate.

Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

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